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VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,588	04/25/97	HAYWARD	N 10441

HM22/0818

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EXAMINER	
SAOUD, C	
ART UNIT	**PAPER NUMBER**
1646	15

DATE MAILED: 08/18/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/765,588	HAYWARD et al.
Examiner	**Group Art Unit**
Christine Saoud	1646

☒ Responsive to communication(s) filed on *Jul 8, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25, 28, 30, 33, 34, and 37-50* is/are pending in the application.

Of the above, claim(s) *1-25, 34, and 37-42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *28, 30, 33, and 43-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. Claims 28, 30 and 33 have been amended, claims 26-27, 29, 31-32 and 35-36 have been canceled, and claims 43-50 have been added as requested in the amendment of paper #14, filed 08 July 1999. Claims 1-25, 28, 30, 33-34, and 37-50 are pending in the instant application.

Claims 1-25, 34 and 37-42 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 11.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 08 July 1999 have been fully considered but they are not deemed to be persuasive.

Oath/Declaration

5. The Declaration stands objected to for the reasons of record in paper #13. Correction is necessary.

Drawings

6. Figures 1-6, 9-11, and 16-17 are still objected to for the reasons of record in paper #13. Correction of the Brief Description of the Drawings will be required when the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(u) (1).

Claim Rejections - 35 USC § 112

7. Claims 47 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 47 and 49 are directed to subject matter of an isolated nucleic acid which has at least about 70% similarity to SEQ ID NO:3 and which hybridizes under low under low stringency conditions to a DNA which encodes a VEGF protein, wherein the hybridization conditions are provided in the specification. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a nucleic acid molecule which encodes a protein of SEQ ID NO:4. This nucleic acid molecule has a nucleic acid sequence of SEQ ID NO:3. The subject matter which is claimed is described above. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a predictability of structure; and/or whether teachings in the application or prior art lead to a

predictability of structure. The claims are directed to nucleic acid molecules which share 70% similarity to a nucleic acid, wherein the nucleic acid molecule hybridizes to a DNA encoding a VEGF protein under low stringency conditions. First, the claims are not limited to nucleic acid molecules encoding a protein with a specific amino acid sequence, and actually do not require the nucleic acid to even encode a protein. The specification contemplates molecules which are VEGF-like but do not have the amino acid sequence of SEQ ID NO:2, including but not limited to, mammalian, bovine, ovine, porcine, equine, rodent, human, birds, fish and reptiles (see page 4 of the specification). The specification only describes one alternatively spliced VEGF protein from human and mouse and fails to teach or describe any other related proteins, let alone from different species or variant forms. Therefore, there is a lack of guidance or teaching regarding structure and function because there are only very limited examples provided in the specification and because there is no guidance found in the prior art. The claims include nucleic acids which share some sequence similarity to the disclosed nucleic acid, however, this sequence similarity is not sufficient to provide the function of encoding a "VEGF-like" protein.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims except for the specific nucleic acid molecules of the Sequence Listing, which are alternatively spliced products of the same gene. The

specification does not provide a complete structure of those nucleic acid molecules which encode the VEGF-like protein and hybridize to the recited sequence under the recited low stringency conditions of the claims. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus (those nucleic acids which hybridize to SEQ ID NO:3 under low stringency conditions) which the specification defines as including different species and variants and the specification teaches a very limited number of embodiment. Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Claims 28, 30, 33, 43, 47-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules which encode naturally occurring VEGF molecules and are capable of inducing vascularization, interacting with a receptor, inducing cell migration, survival, or astroglial cell proliferation, does not reasonably provide enablement for nucleic acid molecules which deviate from the disclosed nucleic acid sequences of the Sequence Listing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Applicant submits that "the specification is directed to molecules which have VEGF-like properties". This is noted and this is also the source of contention with the enablement of the instant invention. The application provides for a nucleic acid molecule which is differentially spliced to provided for several VEGF-like molecules. These VEGF-like proteins have the amino acid sequences of SEQ ID NO:4, 6, 8, and 10. The instant specification does not provide for modification of these proteins or nucleic acid molecules encoding these proteins. The specification contemplates any VEGF molecule which differs from the prior art molecule known as VEGF165 in stating "the molecule of the present invention is VEGF-like or is a homologue of VEGF but comprises an amino acid sequence which is similar but non-identical to the amino acid sequence of VEGF" (see specification at page 4). Embodiments which are included in this definition are species variants, mammalian as well as birds, fish, and reptiles. However, the instant specification fails to provide representative examples which would enable such breadth as what is intended by the specification. Applicant is in essence attempting to claim molecules which have not been made or described in the instant specification. The fact that one of ordinary skill in the art could make a molecule which shares sequence identity to the disclosed sequences is irrelevant because one would not have a reasonable expectation that those molecules which are made would function in the manner required in order to use the molecules. The instant specification provides no guidance as how to modify the disclosed proteins and obtain a protein which has the biological activity of VEGF and no guidance as to which amino acids (i.e. structural elements) of the native proteins are critical to the biological activity. Without this type of guidance, the skilled artisan does not have a reasonable expectation of mutating the VEGF of SEQ ID NO:2 or the nucleic

acid molecule of SEQ ID NO:3 and obtaining a functional protein that retains a biological activity of the native protein, absent evidence to the contrary.

The argument that "standard methods are employed" is basically a "wish to know" and the standard for an enabling disclosure is not one of making and testing. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

9. Claim 49 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a protein wherein the nucleic acid molecule comprises a sequence that encodes a protein, does not reasonably provide enablement for methods which use nucleic acid sequences which hybridize to a disclosed sequence wherein there is no requirement for the hybridizing sequence to encode a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons of record.

Applicant argues that "standard methods are employed to produce recombinant molecules based on expression of referenced nucleotide sequences as well as sequences which hybridize" This argument is not persuasive because in order for the claim to be enabled, the nucleic acid molecule which is to be employed must encode a protein, and **there is no limitation in the claim that requires the hybridizing sequence to encode a protein**. There are a multitude of sequences that would be capable of hybridizing to the disclosed sequence under low stringency

conditions, but they would not be useful in a method of making a protein unless they actually encoded a protein. Furthermore, the instant specification fails to teach how to make a protein with a nucleic acid molecule that does not encode a protein. Therefore, the instant claim is not enabled for the claimed breadth for the reasons provided.

10. Claims 28, 30, 33, 43-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 30, 33, 43, and 47-50 recite (or depend from claims which recite) percent similarity. However, the use of % identity or similarity is indefinite without a recitation of a specific algorithm for calculating this identity. Applicant points to page 15 of the specification for the basis for a specific algorithm to be used. However, the specification does not contemplate a specific algorithm for what is being claimed and there are several algorithms used in the specification. The algorithm at page 15 is but one of many in the specification (see for example page 16, lines 14-16) and this does not provide support for limiting the claims to this particular algorithm because the specification fails to contemplate a claim to % similarity wherein the % similarity is calculated with the algorithm at page 15, absent evidence to the contrary. The instant specification intends % similarity/homology/identity to encompass proteins which are "VEGF-like" and comprises "an amino acid sequence which is similar but non-identical to the amino acid sequence of VEGF", including molecules from livestock animals, companion animals, laboratory animals, and non-mammals such as birds, fish and reptiles (see page 4 of the specification). With

this definition and the use of "similarity" and "homology" in the specification, it is not clear how % similarity is to be calculated in view of the number of different algorithms and the fact that similarity does not mean identity (see attached references of Reeck et al. and Lewin). Because different algorithms will rate "conservative" differences in amino acids differently, it is not clear from the language of the claims of whether "% similarity" would provide for a different value from % identity, and without a specific recitation of which algorithm is to be used, the metes and bounds of the claims cannot be determined.

Claims 43-46 are directed to "isolated nucleic acid encoding or complementary to a sequence", however, the nucleic acid is complementary to another nucleic acid, not to the sequence. The "sequence" is merely a representation of one characteristic of a nucleic acid molecule. The claims are unclear and indefinite because they should be claiming the nucleic acid molecule which is the actual invention, not the sequence of the nucleic acid molecule. A nucleic acid molecule can have sequence encoding a protein, but nucleic acid is complementary to the nucleic acid molecule, not the sequence that the nucleic acid molecule has. The compound or composition which is being claimed is the physical nucleic acid molecule, not the characteristic of a specific sequence. This ground of rejection can be obviated by replacing "sequence" with "nucleic acid molecule" or "nucleic acid". Please be sure to also amend the dependent claims to provide proper antecedent basis for the new language if necessary.

Claim 36 is confusing in that it is not clear what the constitution of "the nucleotide sequence" is from the claim. The claim recites that the nucleotide sequence is "as set forth in

SEQ ID NO:3", but then further states that "the nucleotide sequence has at least 15% similarity but at least 30% dissimilarity to the nucleotide sequence set forth in SEQ ID NO:3". Therefore, it is not clear if "the nucleotide sequence" has the sequence of SEQ ID NO:3 or if it is different from that sequence, making the claim indefinite.

Claim Objections

11. Claim 49 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 49 depends from claim 48. Claim 48 requires the use of a nucleic acid which encodes a polypeptide having at least about 90% similarity to SEQ ID NO:2. Claim 49 attempts to further limit the method of 48 by using a nucleic acid which comprises SEQ ID NO:3. However, the polypeptide that is encoded by SEQ ID NO:3 is only about 30% identical to that of SEQ ID NO:2 (see Table 2.2 of the specification at page 18). Therefore, claim 49 does not further limit the subject matter of claim 48 and is improperly dependent.

Claim Rejections - 35 USC § 102

12. Claims 28, 30, 43 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al. (Science 246: 1306-1309.

The instant claims require a nucleic acid which encodes a polypeptide which comprises an amino acid sequence of SEQ ID NO:2 (or has at least about 90% similarity thereto). The nucleic acid of Leung et al. encodes a polypeptide which has the exact amino acid sequence of SEQ ID NO:2. This nucleic acid of Figure 1B anticipates the instant claims. Leung et al. do not disclose the property of inducing astroglial proliferation, however, this property would be expected to be inherent to the nucleic acid of Leung et al. since it meets the functional limitations of the claims, absent evidence to the contrary.

Leung et al. additionally expressed the nucleic acid encoding the VEGF and isolated the protein that was produced (see Figure 4 and legend for Figure 4). Therefore, the limitations of claim 48 are also met by Leung et al.

13. Claims 44 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Eriksson et al. (U.S. Pat. No. 5,607,918).

Eriksson et al. teach a nucleic acid (SEQ ID NO:11) which comprises the nucleotide sequence of SEQ ID NO:4 and 10 of the instant claims, and therefore anticipates the claims. Eriksson et al. claims priority to U.S.S.N. 08/397,651, which has a filing date of 01 March 1995, and therefore, constitutes prior art against the instant application. Applicant has raised the question of whether Eriksson et al. is entitled to benefit of 08/397,651. The application of '651 is not available at this time for inspection, therefore the rejection will be maintained until such a time when the '651 application can be inspected and the issue of priority is resolved.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 16, 1999

CHRISTINE SAOUD
PATENT EXAMINER

Christine Saoud